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Correlation between Vitamin D deficiency and Pre-diabetes in Arar, Saudi Arabia

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Abstract
Aim: Prediabetes is implicated in obesity, fatty liver disease and metabolic syndrome and an increased risk of type 2 diabetes (T2DM). This case-control study aimed at finding a correlation between vitamin D (VitD) deficiency and prediabetes.
Material and Methods: Sixty participants (age >30 years) were selected. Thirty of them comprised of prediabetic subjects and thirty were normoglycemic healthy controls. The subjects suffering of kidney, heart, liver and autoimmune diseases, diabetes, and pregnancy were not included. Plasma VitD (measured as 25-hydroxycholecalciferol; 25-OH-VitD) and fasting plasma glucose (FPG) levels were assessed immunometrically and colorimetrically, respectively.
Results: The results showed that prediabetic subjects had significantly lower plasma levels of 25-OH-VitD (P = 0.000) compared to normoglycemic controls; where their median levels were 17.68 and 31.72 mmol/L, respectively with a strong negative correlation against FPG (r = -0.649, P = 0.000) and a high odds ratio (OR) of 4.078.
Discussion: The study found a significant inverse correlation between plasma VitD and FPG levels in prediabetic subjects. The high OR for VitD deficiency in the normoglycemic and prediabetic participants suggests a strong possibility of a causal link between low plasma VitD levels and prediabetes, as major risk factor for T2DM.

Keywords
Vitamin D; Pre-Diabetes; HbA1C; Fasting Plasma Glucose

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Introduction

The relationship between vitamin D (VitD) deficiency and the development of type 2 diabetes mellitus (T2DM) has been established by previously published research. Several studies have found a correlation between low VitD level and diabetes mellitus [1-4]. However, the evidence for direct causal link between VitD deficiency and diabetes mellitus is contradictory, and further studies are still necessary since only a limited number of studies using the human model have been conducted so far [5,6].

Prediabetes is a transition stage between normoglycemia and T2DM. A person is considered prediabetic when his/her blood glucose level is increased above normal but is still not high enough to be classified as diabetes. Based on WHO criterion, prediabetes is diagnosed as having a fasting blood glucose level of 110 - 125 mg/dL, and, based on American Diabetes Association criterion, fasting blood glucose level of 100 - 125 mg/dL/5.6 - 6.9 mmol/L is diagnostic [7]. The onset of prediabetes occurs when the body manifests insulin resistance or becomes unable to utilize insulin. Risk factors for prediabetes include family history of full diabetes, obesity, cardiovascular disease, increased serum triglycerides, lowered serum HDL-cholesterol, raised blood pressure, and elevated plasma glucose fasting level. Factors in females also include those having polycystic ovarian syndrome or gestational diabetes.

Pittas et al. [1] have reported a correlation between fasting plasma glucose (FPG) level and VitD deficiency. Insulin resistance was documented using the Homeostatic Model Assessment-Insulin Resistance (HOMA-IR) for subjects exhibiting prediabetes [8]. A separate study had correlated VitD deficiency and prediabetes. Subsequently, they intervened utilizing VitD supplements. However, no significant change in either insulin sensitivity or progression into diabetes, although glycated hemoglobin (HbA1C) was found to be significantly decreased [9]. Another Indian study reported a decrease in both FPG and insulin resistance along with inflammatory markers among those taking VitD supplements [10]. The current study investigated a possible correlation between low VitD levels and the high prevalence of prediabetes among population in Arar, Saudi Arabia.

Material and Methods

Setting and Participants:

The protocols used in this study were in line with the ethical standards laid down by the Arar Central Hospital, Arar, Saudi Arabia, and in accordance with the Helsinki Declaration of 1975 that was revised in 2013. The study was conducted from January to March 2017. It recruited 60 participants of both genders aging ≥30 years. They were selected by sequential enrollment from those visiting/working in Arar Central Hospital, Arar, Saudi Arabia.

Inclusion criteria were the classic symptoms of prediabetes such as increased thirst, polyuria, fatigue and blurred vision on top of the diagnostic FPG levels. The research participants were categorized into two groups: 30 prediabetic subjects and 30 healthy normoglycemic controls after careful clinical assessment to meet all the inclusion criteria shown in Table 1. The gender distribution of the subjects was 76.7% females and 23.3% males. There was no difference in age between prediabetic subjects and controls. The median age of the research subjects was 45 and 43.8 years for males and females, respectively.

Based on the measured FPG level, the patients were divided into two groups. Patients exhibiting diabetes mellitus, immobilized, or autoimmune, renal, liver and heart diseases were excluded from the study. In addition, pregnant female subjects and those using VitD supplements were excluded. All subjects exhibiting VitD levels <20 ng/mL (<50 nmol/L) were considered VitD deficient, while subjects with FPG of 100 - 126 mg/dL (5.6 - 6.9 mmol/L) were considered prediabetic. After a 12-hour overnight fast, 3 mL of venous blood samples were collected to recover plasma. The samples were then analyzed for FPG and VitD levels.

Measurement of FPG Level:

FPG measurements are the basis for the diagnosis of T2DM, idiopathic hypoglycemia, neonatal hypoglycemia and pancreatic islet cell carcinoma. In this study, FPG was measured by the enzymatic colorimetric test using the BS-400® Chemistry Analyzer (Mindray Medical Int. Ltd, Shenzhen, China).

Measurement of Vitamin D Level:

Both VitD2 and D3 are carried in the blood plasma as complex with the VitD-binding protein. VitD is carried to the liver to be hydroxylated into calcifediol (25-hydroxycholecalciferol; 25-OH-VitD). 25-OH-VitD represents the main storage form of VitD in the body. Its concentration in the blood is used for assessing the overall VitD status. For the purpose of this study, 25-OH-VitD levels were determined using the Elecsys Vitamin D Total Assay that demonstrated a high degree of comparability to the LC-MS-MS with a minimum detection limit of <5 ng/mL (Roche Diagnostics International AG, Rotkreuz, Switzerland).

Statistical Analysis:

Statistical Analysis was performed with SPSS v.23 (Chicago, USA). Mean VitD levels were compared in prediabetic and normoglycemic subjects. The frequency for different age groups was expressed as a percentage. Pearson correlation analysis was done to check the relationship with FPG and odds ratio (OR) was used to quantify the possible causal association between VitD deficiency and prediabetes.

Results

Prediabetic subjects were found to have significantly lower levels of VitD (median plasma level of 17.68) compared to normoglycemic healthy participants (median plasma level of 31.72 nmol/L; P = 0.000), respectively (Table 1). Pearson correlation analysis showed a significant inverse correlation between plasma VitD and FPG levels (r = -0.649, P = 0.000) in the prediabetic groups, as shown in Table 2. The odds ratio (OR) for VitD deficiency in normoglycemic and prediabetic groups was found to be 4.078 (P <0.0001), which suggests a strong possibility of a plausibly causal link between low VitD levels and prediabetes (Table 2).

Discussion

It is already known that polymorphisms in the VitD receptor gene and the resulting inefficiency of VitD and/or VitD deficiency can lead to the development of diabetes mellitus [11-20]. The

Table 1. Characteristics and plasma vitamin D (measured as 25-hydroxycholecalciferol; 25-OH-VitD) and fasting plasma glucose (FPG) levels of the normoglycemic healthy controls and the prediabetic subjects investigated

Parameter	Pre-diabetic Subjects	Normoglycemic Controls	P-value
Number; n	30	30	-
Gender; n (%)			
Male	7 (23.3)	3 (10)	-
Female	23 (76.7)	27 (90)	
Age years; Median	45	43.8	0.000
FPG mmol/L; Median	5.96	4.91	0.000
25-OH-VitD; nmol/L			
Range	15.81 - 19.55	29.46 - 33.98	0.000
Median	17.68	31.72	

Table 2. Pearson correlation, Odds Ratio (OR) and 95% Confidence Intervals (CIs) analysis of the relationship between plasma vitamin D (measured as 25-hydroxycholecalciferol; 25-OH-VitD) and fasting plasma glucose (FPG) levels among healthy controls and prediabetic subjects

	FPG	25-OH-VitD	OR	CIs
FPG			4.078	3.330, 4.312
r	1	-0.649		
P-value	-	0.000		
n	60	60		
25-OH-VitD				
r	-0.649	1		
P-value	0.000	-		
n	60	60		

activated VitD receptor controls gene expression and ensures that intracellular levels of Ca+2 and reactive oxygen species are maintained at normally low physiological levels. This harmonizes the homeostasis of several metabolic and immunological activities towards the prevention of diabetes mellitus [21]. Prediabetes is an early stage of diabetes and considered to be a significant risk factor for development of microvascular and cardiovascular disorders, along with complications arising from T2DM such as nephropathy, neuropathy and retinopathy [22]. In the current study, the samples were acquired from the population of the Northern Border Region of Arar, Saudi Arabia, and the VitD levels were measured to estimate the possible correlation with prediabetes. It was found that prediabetic subjects have significantly low levels of VitD in comparison with those of normoglycemic healthy controls. A significant inverse correlation was seen between plasma VitD and FPG levels, as shown in Table 2. The odds ratio of 4.078 for VitD deficiency in the normoglycemic and prediabetic groups suggests a strong possibility of a causal link between low VitD levels and prediabetes (Table 2).

The findings of this study correspond with those obtained by Qurrat-ul-Ain et al. [23] who reported that low VitD levels correlates with glucose intolerance in adults. Another study by Pinelli [24], comprising Arab Americans, reported that males with glucose intolerance tend to have reduced levels of VitD. Other studies report varying modes of correlation between VitD level and prediabetes. According to the data reported by NHANES III, non-Hispanic blacks show no correlation between the two parameters. Furthermore, one study in Finland involving 7503 subjects has shown that high levels of VitD lowered the incidence of diabetes by 72% among males. However, it showed no significant change among females after adjustment for T2DM risk factors [25].

Discrepancy between the findings of this study and the previously published studies can be explained by taking into consideration the differences between the participants in terms of ethnicity, body mass index, and other environmental/life style factors that contribute to low VitD levels and high blood glucose levels [22]. The negative correlation of VitD deficiency with prediabetes with a high OR found here causally involve VitD level in blood glucose regulation, prediabetes and diabetes. However, the influence of VitD level on glucose metabolism may also depend on other factors such as ethnic and genetic background, gender, obesity and co-morbidities [1].

Conclusions

VitD deficiency causes an increase in the concentration of intracellular Ca+2 and Reactive Oxygen Species, which causes a decline in the Insulin signaling pathway, insulin resistance, prediabetes and the onset of diabetes. The results from this study prove that the mean plasma VitD level of prediabetic and normoglycemic subjects is significantly different and negatively correlated with FPG. A causal relationship for such deficiency was inferred from the high OR. This suggests that people with VitD deficiency carry a greater risk for developing T2DM, and indicates the need for VitD supplementation of the general population and prediabetic subjects in particular.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

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